REMARKS

I. Previously filed Response and Supplemental Reponse

Applicant filed a Response on November 22, 2009 ("November 2009 Response") and a Supplemental Response on December 22, 2009 ("December 2009 Supplmental Response). Both the November 2009 Response and the December 2009 Supplemental Response were filed before the Office Action mailed on November 27, 2009 was mailed. However, the November 2009 Response and the December 2009 Supplemental Response were not considered. Accordingly, Applicant submits the present response to address the Office Action mailed on November 27, 2010 and incorporates the November 2009 Response and the December 2009 Supplemental Response.

II. Present Claims

The present claims are drawn to methods for treating pain with spogosine. Applicant has suprising discovered that spongosine can be safely used to treat pain. As the specification explains at page 2, certain A1 adenosine receptor agonists have been found have analgesic activity and certain A2 adenosine receptor agonists have been found anti-inflammatory activity. However, as also explained at page 2 of the specification, A1 receptor agonists are known cause bradycardia and A2 adenine receptor agonists are known cause vasodilatation leading to hypotension and tachycardia. For these reasons, adenosine receptor agonists were commonly considered to have limited usefulness in treatment of pain. Despite these teachings, which would discourage one from investigating adenosine receptor agonists, particularly spongosine, which was shown by Ueeda et al. have dangerous side effects, for treatment of pain, Applicants discovered that spongosine can be used to safely and effectively treatment pain in human patients.

III. Amendment of the claims in the previously filed RCE

Applicant previosuly filed an RCE accompanied by an amendment that amended claim 11 to specify that the subject is a human subject. No new matter was added by this amendment.

IV. Anticipation Rejection under 35 U.S.C. § 102(b)

Claims 11-14, 16, 17, 19-31 and 47-52 were rejected under 35 U.S.C. § 102(b) as being anticipated by Bartlett et al. (*J. Med. Chem.* 24:947-954, 1981) The Examiner stated that Bartlett et al. discloses administration of spongosine to treat carrageenan-induced inflammation. The Examiner argued that this treatment must have inherently resulted in the suppression of pain.

Bartlett et al. does not describe administration of spongosine to a human subject, as required by claim 11. Thus, irrespective of whether the administration of spongosine to rats at a level that reduced inflammation resulted in inherent treatment pain, Bartlett et al. cannot anticipate any of the pending claims, all of which depend directly or indirectly from claim 11, which now recites treatment of a human subject.

In view of the forgoing, Applicant respectfully requests that the rejections under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

V. Obviousness Rejection under 35 U.S.C. § 103(a)

Bartlett et al. and Herrick-Davis et al.

Claims 11-14, 16, 17, 19-31 and 47-52 were rejected under 35 U.S.C. § 103(a) as being obvious in view Bartlett et al. and Herrick-Davis et al. (*European Journal of Pharmacology*, 162:365-369, 1989).

The Examiner stated that Herrick-Davis et al. discloses that a variety of adenosine analogues that are known in the art to be adenosine receptor agonists and have been found to be analgesic agents with efficacy comparable to morphine. The Examiner argued that one of the compounds tested, 2-chloroadenosine (CADO), is a close structural relative to spongosine. The Examiner argued that it would have been obvious "to conclude that compounds very closely analogous to CADO disclosed to be a potent analgesic by Herrick-Davis et al. to be consistent

with an analgesic effect of spongosine as disclosed by Bartlett et al. in the treatment of an inflammatory response." The Examiner argued that one of ordinary skill in the art would have been motivated to combine these references because both references are directed to disclosures of the analgesic effects observed following the administration of 2-substituted analogues of adenosine, including spongosine.

Applicant respectfully traverses this rejection. However, before discussing the rejection in detail, Applicant respectfully points out that, contrary to the implication in the statement by the Examiner quoted above, Bartlett et al. does not disclose any analgesic effect of spongosine – only an anti-inflammatory effect is disclosed.

Structurally similar compounds do not necessarily exhibit similar properties

It is well established that structural similarity does not give rise to obviousness in the absence of similar properties ("it is not structural similarity alone that gives rise to obviousness, but the concomitant assumption that the structurally similar compounds will have like properties." *Ex Parte Chwang* 231 USPQ 751, 752 (Bd. Pat. App. & Int'f 1986). In the present case, the art teaches that CADO has properties that differ from structurally related compounds.

CADO is shown in Ueeda et al. (*Life Sciences* 49:1351-1358) to have substantially different binding constants at A_1A and A_2A receptors as compared with 2-ethoxyadenosine. In particular, the inhibition constant K_i of CADO (#3) at A_1AR differs from that for 2-ethoxyadenosine (#13) by a factor of 132 in rat and 170 in guinea pig. Furthermore, according to Ueeda et al., 2-ethoxyadenosine (#13) is selective for the A_2AR receptor, whereas compounds including CADO (#3) are unselective (Ueeda et al., page 1354, lines 3-4). Consequently, because the Ueeda et al. reference teaches that there are substantial differences between 2-ethoxyadenosine and CADO, one of ordinary skill in the art would not expect another 2-alkoxyadenosine such as spongosine (2-methoxyadenosine) to have similar properties to CADO. Contrary to the Examiner's allegation, one of ordinary skill in the art would not view CADO as closely analogous to spongosine. Thus, disclosure of CADO as an analgesic in Herrick-Davis et al. does not support an obviousness rejection of the claimed method of treating pain which comprises administering spongosine (2-methoxyadenosine) to a human subject in need of such treatment.

Even assuming spongosine exhibited properties similar to CADO, one would avoid its use in treatment of humans

Moreover, even if one were to assume that CADO and spongosine have similar properties, one would not be motivated to use spongosine for treatment of pain in humans.

This is because Ueeda et al. teach that at a dose at which spongosine reduced inflammation by 25%, blood pressure dropped by a striking 41% and heart rate by 25%. Clearly, such side effects would not be even remotely tolerable in the treatment of pain in humans. Thus, one skilled in the art would not consider using spongosine for treatment of pain even if one assumed that spongosine had analgesic properties similar to those of CADO.

Moreover, Bartlett et al. suggest that the harmful side effects observed with adenosine analogues consistently accompany anti-inflammatory activity: "The muscle relaxant, hypothermic, and hypotensive effects of 1-methylisoguanosine, as well as a number of the analogue, were accompanied by a decrease in heart rate. **None of the analogues investigated had any selectively of action whereby the bradycardia [reduced heart rate] could be removed or reduced while maintaining the other pharmacological effects.**" (Bartlett et al. at 950; emphasis added). Given the detrimental side effects observed by Ueeda et al. and given that the side effects are observed with several adenosine analogues that have anti-inflammatory activity, one of ordinary skill in the art would not be motivated to use spongosine to treat pain in humans. Indeed, one skilled in the art would endeavor to avoid the use of spongosine.

For the forgoing reasons, Applicant respectfully requests that the rejections under 35 U.S.C. §103 be reconsidered and withdrawn.

Applicant surprisingly found that spongosine can be used to safely treat pain and can do so at a dose that gives rise to a plasma concentration below the Kd for the adenosine receptor

As the specification explains at page 2, certain A1 adenosine receptor agonists have been found have analgesic activity and certain A2 adenosine receptor agonists have anti-inflammatory activity. However, as also explained at page 2 of the specification, A1 receptor agonists cause bradycardia and A2 adenine receptor agonists cause vasodilatation leading to hypotension and

tachycardia. For these reasons, adenosine receptor agonists were commonly considered to have limited usefulness in treatment of pain.

Despite these teachings, which would discourage one from investigating adenosine receptor agonists, particularly spongosine, which was shown by Bartlett et al. have dangerous side effects, for treatment of pain, Applicants discovered that spongosine can be used to safely and effectively treatment pain in human patients. In addition, Applicants surprisingly found that spongosine can be used to treat pain even when administered at a very low dose. As the specification explains at page 9, spongosine was "effective in inhibiting pain perception in mammals suffering from neuropathic and inflammatory pain even when administered at doses expected to give concentrations well below those known to activate adenosine receptors."

Spongosine can effectively reduce pain when administered at a dosage that results in a plasma concentration that is far lower than that which would be expected to be required to activate the A1 and A2A adenosine receptors

The attached Declaration of Peter Richardson, Ph.D., under 35 U.S.C. §1.132 presents data demonstrating that spongosine can effectively reduce pain when administered at a dosage that results in a plasma concentration that is far lower than that which would be expected to be required to activate the A1 and A2A adenosine receptors.

In his Declaration, Dr. Richardson states that he supervised a study which found that spongosine can reduce inflammatory and neuropathic pain in animals at a dose of 0.4 mg/kg pain and a study which found that spongosine can reduce diabetic neuropathic pain in humans at a dose of 0.1mg/kg. Dr. Richardson goes on to state that the dosages used result in a peak maximum plasma concentration of about 0.2 micromolar, an order of magnitude below the Kd for spongosine at the A2A adenosine receptor (about 2.0 micromolar). As Dr. Richardson explains, one would expect that at a plasma concentration so far below the Kd of spongosine for the A1 and A2A adenosine receptor, spongosine would not activate either receptor and thus would not have an analgesic effect.

In his Declaration, Dr. Richardson explains that it appears that in certain tissues, such as epithelia; tissue damaged by physical, chemical or biological trauma; and tissues undergoing an inflammatory response, the pH is lower than that of other tissues. This lower pH alters the

binding affinity of spongosine for adenosine receptors such that spongosine is selective for the A2A adenosine receptor in such tissues. This allows the unexpected alleviation of pain and inflammation by spongosine at a plasma concentration that is too low to activate A1 and A2A adenosine receptors in other tissues thereby avoiding such negative side-effects as bradycardia and hypotension respectively.

As is evident from the Declaration of Peter Richardson Under 35 U.S.C. §1.132, spongosine can unexpectedly relieve pain at dosages that are far below that which would be expected to be needed to activate the adenosine A2A receptor. In addition, spongosine can relieve pain without causing dangerous bradycardia and hypotension. These results are unexpected in view of the prior art teachings, e.g., in Bartlett et al., that spongosine causes bradycardia and hypotension.

In view of the forgoing, even if the presently claimed invention were *prima facie* obvious in view of the cited references, which it is not, Applicant's unexpected results are more than sufficient to overcome the *prima facie* case. For this reason, Applicant respectfully requests that the rejections under 35 U.S.C. §103 be reconsidered and withdrawn.

Fukunaga and Sollevi Patents

In rejecting claims 11-14, 16, 17, 19-31 and 47-52 as obvious in view Bartlett et al. and Herrick-Davis et al., the Examiner stated that "Herrick-Davis et al. has additional support in the form of the previously cited Fukunaga patent reference, the newly cited Fukunaga patent references, and the newly cited Sollevi patent references, all of which disclose that adenosine has been established to have analgesic activity". The Examiner went on to state that "the question of a correlation between analgesic activity and 2-substitution in adenosine and adenosine analogues suggests that small 2-substituents may not have much effect on the analgesic activity of adenosine, and therefore that 2-substituted analogues of adenosine can be expected to have analgesic activity similar to that of adenosine itself."

Applicant respectfully requests that the Examiner clarify whether the Examiner is rejecting any of the pending claims as obvious in view of any of the Fukunaga or Sollevi patents noted on the PTO-892 form accompanying the Office Action. If so, Applicant respectfully

requests that the Examiner state the claims being rejected and combination of references that forms the basis of the rejection so that Applicant can respond to the rejection.

While it unclear whether the Examiner is rejecting any of the pending claims based on Fukunaga and Sollevi, it does appear the Examiner believes that these references suggest that substitution at the 2 position of the adenine ring of adenosine does not impact analgesic properties. Of course, the same reasoning would suggest that substitution at the 2 position of the adenine ring does not impact other properties. However, according to Fukunaga '209, adenosine has a half-life in the human body of just a few seconds. In contrast, the half-life of spongosine in the human body is far, far longer – about 1 hour and 40 minutes (see Declaration of Peter Richardson, Ph.D., enclosed herewith). Moreover, as discussed above in regard to Uedda, substitution at the 2 position of the adenine ring can dramatically impact receptor binding. Thus, 2-ethoxy adenosine is selective for the A2 receptor over the A1 receptor whereas CADO is non-selective. Applicant reserves the right to comment further on the Fukunaga and Sollevi references should the Examiner actually base a rejection on one or more these references.

VI. Enablement Rejection under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 11-14, 16, 17, 19-31 and 47-52 for lack of enablement. The Examiner stated that while the specification is enabling "for the treatment of inflammation, hypertension, and pain by the administration of spongosine, or a combination of spongosine and the amino acid gabapentin, does not reasonably provide enablement for the treatment of any of the noted conditions with other mixtures of spongosine and another analgesic acid as disclosed in claims 27 and 28.

Except for claims 27 and 28, the pending claims do not recite the administration of an agent other than spongosine. Accordingly, Applicant respectfully requests that, the Examiner withdraw this rejection as applied to claims 11-14, 16, 17, 19-26, 29-31 and 47-52.

Regarding claims 27 (which recites an analgesic agent in combination to spongosine) and 28 (which recites specific classes of analgesic agents in combination with spongosine), it is Applicant's position that those skilled in the art are aware of many, many analgesic agents and would know how to treat patients with these analgesic agents. In view of this, it is Applicant's

position that claims 27 and 28 are enabled, and Applicant requests that the rejection of claims 27 and 28 under 35 U.S.C. §112, first paragraph for lack of enablement be withdrawn.

VI. Written Description Rejection under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 47-50 as allegedly failing to meet the written description requirement. These claims have been cancelled. In view of the forgoing, Applicant respectfully requests that this rejection be withdrawn.

VII. Obviousness-type double patenting rejections

The Examiner provisionally rejected claims 11-14, 16, 17, 19-31 and 47-52 under the judicially created doctrine of obviousness type double patenting over claims 16-33 of co-pending Application Ser. No. 10/547,455, filed March 5, 2004, and claims 13-24 of co-pending Application Ser. No. 10/547,454, filed March 5, 2004.

Applicant will address any obviousness type patenting rejections upon notification that there are claims in the current application which are otherwise allowable.

CONCLUSION

For the reasons set forth above, Applicants submit that the claims of the instant application, as amended herein, are in condition for allowance. Reconsideration and withdrawal of the Examiner's objections and rejections are hereby requested. Allowance of the claims is earnestly solicited.

In the event that a telephone conversation could expedite the prosecution of this application, the Examiner is requested to call the undersigned at 617.542.5070.

No fee is believed to be due. If, however, there are any charges or credits, please apply them to Deposit Account No. 06-1050.

Respectfully submitted,

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